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CHEMICAL ABSTRACTS, vol. 103, no. 25, 23rd December 1985, page 677, abstract no. 212685x, Columbus, Ohio, US; S.D. BRINKMAN et al.: "Lithium-induced increases in red blood cell choline and memory performance in Alzheimer-type dementia", & BIOL. PSYCHIATRY 1984, 19(2), 157-64

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- (73) Proprietor: SCOTIA PHARMACEUTICALS LIMITED
Efamol House Woodbridge Meadows
Guildford Surrey GU1 1BA(GB)
(72) Inventor: Horrobin, David Frederick
2e Cedar Lodge Lythe Hill Park
Haslemere Surrey(GB)
(74) Representative: Cockbain, Julian Roderick
Michaelson et al
Frank B. Dehn & Co. European Patent Attorneys Imperial House 15-19, Kingsway
London WC2B 6UZ(GB)

EP 0 234 733 B1

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Description

This invention relates to the use of substances for the manufacture of therapeutic agents for use in treatment and to pharmaceutical compositions for use in treatment as defined below in more detail.

- 5 Dementia and especially Alzheimer's disease may involve progressive deterioration of brain function resulting in a loss of the individual's ability to lead a normal life. It may occur prematurely in the subject's 50's or earlier and may appear as an unusually severe acceleration of normal ageing.

At present the cause of Alzheimer's disease is unknown and there is no certain treatment.

- Our investigations suggest that dementias such as Alzheimer's disease are related to an imbalance in
 10 the conversion of essential fatty acids (EFAs) to prostaglandins (PGs). In normal ageing, red cell membrane fluidity decreases (i.e. the membrane becomes stiffer) and the production of cyclic adenosine monophosphate (AMP) by cells such as lymphocytes declines. The changes in Alzheimer's disease are diametrically opposite, with an unexpected increase in cell membrane fluidity and a rise in cyclic AMP levels occurring. Certain PGs, such as PGE₁ (formed from dihomogammalinolenic acid (DGLA)), PGI₂ -
 15 (formed from arachidonic acid (AA)) and PGI₃ (formed from eicosapentaenoic acid (EPA)) are known to be able to increase membrane fluidity and cyclic AMP levels. Thus we believe that the unexpected changes in Alzheimer's disease could be explained as arising from excessive conversion of EFAs to PGs. The EFAs are essential components of the structure of all cell membranes in the body, particularly of those in the brain in which EFA levels are exceptionally high. An uncontrolled and excessive conversion of EFAs from
 20 the cell membranes, where they are primarily found in the phospholipid form, into PGs would be expected to lead to structural damage to and functional impairment of cell membrane function. This is however only offered as a possible theoretical explanation and the utility of the present invention is not of course dependant on this explanation being correct.

- It is an object of the present invention to provide the use of certain materials for the manufacture of a
 25 therapeutic agent for treating subjects to combat dementias such as Alzheimer's disease.

In one aspect the invention provides the use of an essential fatty acid or a physiologically acceptable salt thereof, preferably together with a physiologically acceptable lithium compound, for the manufacture of a therapeutic agent for combatting presenile or senile dementia, in particular Alzheimer's disease.

- Besides acting as PG bioprecursors, the EFAs are themselves important in the body chemistry and
 30 EFA depletion may be responsible for certain effects of dementias such as Alzheimer's disease. Thus following the invention EFAs may be administered to the subject, conveniently orally or parenterally, if desired simultaneously or in conjunction with the administration of a lithium compound. Indeed, in view of the risks of EFA depletion, the EFAs may be administered to patients suffering from Alzheimer's disease even in the absence of lithium treatment.

- 35 The term "essential fatty acids" is used herein in its conventional sense to refer to the two fatty acid series comprising linoleic acid (LA), gamma-linolenic acid (GLA), dihomogammalinolenic acid (DGLA), arachidonic acid (AA), adrenic acid and 22:5n-6 and alpha-linolenic acid (ALA), 18:4n-3, 20:4n-3, eicosapentaenoic acid (EPA), 22:5n-3 and docosahexaenoic acid (DHA).

- Particularly preferred EFAs for administration according to the invention are DGLA, AA, EPA, DHA, LA,
 40 GLA, ALA and 18:4n-3. For the purposes of the present invention, a particularly suitable source of GLA and LA is found in evening primrose oil. Where the EFA is administered in the form of a salt thereof, it is particularly preferred to employ the lithium salt as one salt will thus provide both active ingredients. Daily dosages of the EFAs will again be dependent on factors such as body weight and the severity of the condition but will generally be in the range 1 mg to 200 g for the adult human. For LA and ALA, daily
 45 dosages are preferably 100 mg to 200 g, especially preferably 2-30 g, while for other fatty acids such as GLA, DGLA, AA, 18:4n-3, EPA and DHA daily dosages will preferably be 1 mg to 50 g, especially preferably 20 mg to 10 g.

- Lithium compounds are used according to the present invention in view of their ability to reduce production of cyclic AMP and to inhibit the metabolic conversion of EFAs to PGs, in part by inhibiting the
 50 metabolism of phosphatidylinositol. Administration of lithium may therefore serve to correct any imbalance in the conversion of EFAs to PGs and thus be of benefit in the treatment of dementia and in particular of Alzheimer's disease.

- The administration of the lithium compound following the invention is conveniently parenteral or, preferably, oral and the compound, which is in a form from which lithium ions are biologically accessible, is
 55 preferably a salt such as the carbonate, citrate, succinate, chloride, bromide, acetate, acetylsalicylate, benzoate, bitartrate, nitrate, selenate, selenite, sulphate, aspartate, gluconate or thenoate.

The daily dosage of the lithium compound for the adult human will generally be in the range of 5 to 2000 mg, preferably 20-600 mg, especially 50-600 mg of lithium ions although precise dosages will depend

upon factors such as the patient's body weight and the severity of the condition. The lithium plasma level will generally be monitored and the rate of administration adjusted to provide a suitable concentration in the plasma, e.g. of 0.05 to 1.6 mM lithium per litre.

According to the invention there may be manufactured a pharmaceutical composition for combatting presenile or senile dementia, in particular Alzheimer's disease and comprising as active ingredient an essential fatty acid or a physiologically acceptable salt thereof, and preferably also a physiologically acceptable lithium compound, conveniently together with at least one pharmaceutical carrier or excipient.

The pharmaceutical compositions manufactured according to the present invention are preferably in dosage unit form, e.g. in the form of tablets, coated tablets, capsules etc, advantageously containing 50 to 1200 mg of EFA or salts thereof and optionally 100 to 1200 mg of the lithium compound.

The following Examples serve to illustrate compositions which may be manufactured according to the invention:

Example 1 - Capsules

Capsules are prepared by conventional methods using conventional aids, (e.g. gelatin cases) and with the following active ingredients per capsule:

<u>Capsule No.</u>	<u>Lithium Salt</u>	<u>EFA</u>
1	-	Evening primrose oil* (500 mg)
2	-	DGLA (50mg)
		AA (50mg)
		EPA (50mg)
		DHA (50mg)
3	Succinate (200 mg)	GLA (45 mg)
		LA (360 mg)
4	Carbonate (250 mg)	GLA (50 mg)
		LA (200 mg)
		ALA (10 mg)
		18:4n-3 (20 mg)
5	Citrate (200 mg)	EPA (25 mg)
		DHA (30 mg)
		GLA (40 mg)
6	Lithium Gammalinolenate	(1000mg)
7	Lithium Gammalinolenate	(500mg)
	Lithium Eicosapentaenoate	(500mg)

* containing GLA (45 mg) and LA (360 mg)

Claims

1. The use of an essential fatty acid or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for combatting presenile or senile dementia.
2. Use as claimed in claim 1 for the manufacture of a therapeutic agent for combatting Alzheimer's

disease.

3. Use as claimed in either one of claims 1 and 2 wherein said essential fatty acid or salt thereof is selected from dihomogammalinolenic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, linoleic acid, gammalinolenic acid, alphalinolenic acid, 18:4n-3 and physiologically acceptable salts thereof.
4. Use as claimed in any one of claims 1 to 3 of a physiologically acceptable lithium compound together with said essential fatty acid or salt thereof.
5. Use as claimed in claim 4 wherein said lithium compound is a lithium salt.
6. Use as claimed in claim 5 wherein said lithium salt is selected from: lithium carbonate, lithium citrate, lithium succinate, lithium chloride, lithium bromide, lithium acetate, lithium acetylsalicylate, lithium benzoate, lithium bitartrate, lithium nitrate, lithium selenate, lithium selenite, lithium sulphate, lithium aspartate, lithium gluconate and lithium thenoate.
7. Use as claimed in claim any one of claims 1 to 6 of a lithium salt of an essential fatty acid.
8. Use as claimed in any one of claims 4 to 7 for the manufacture of said agent in dosage unit form each dosage unit containing from 100 to 1200 mg of said lithium compound.
9. Use as claimed in any one of claims 1 to 8 for the manufacture of said agent in dosage unit form each dosage unit containing 50 to 1200 mg of said essential fatty acid or salt thereof.

Revendications

1. Utilisation d'un acide gras essentiel ou d'un sel physiologiquement acceptable de ce dernier pour la préparation d'un agent thérapeutique destiné à combattre la démence sénile ou présénile.
2. Utilisation suivant la revendication 1 pour la préparation d'un agent thérapeutique destiné à combattre la maladie d'Alzheimer.
3. Utilisation suivant l'une quelconque des revendications 1 et 2, caractérisé en ce que l'on choisit l'acide gras essentiel ou le sel de ce dernier parmi l'acide dihomogammalinoléique, l'acide arachidonique, l'acide éicosapentaénoïque, l'acide docosahexaénoïque, l'acide linoléique, l'acide gammalinoléique, l'acide alphalinoléique, 18:4n-3 et les sels physiologiquement acceptables de ces composés.
4. Utilisation suivant l'une quelconque des revendications 1 à 3 d'un composé de lithium physiologiquement acceptable, en association avec l'acide gras essentiel précité, ou un sel de celui-ci.
5. Utilisation suivant la revendication 4, caractérisé en ce que le composé de lithium précité est un sel de lithium.
6. Utilisation suivant la revendication 5, caractérisé en ce que l'on choisit le sel de lithium précité parmi le carbonate de lithium, le citrate de lithium, le succinate de lithium, le chlorure de lithium, le bromure de lithium, l'acétate de lithium, l'acétylsalicylate de lithium, le benzoate de lithium, le bitartrate de lithium, le nitrate de lithium, le sélénate de lithium, le sélénite de lithium, le sulfate de lithium, l'aspartate de lithium, le gluconate de lithium et le thénate de lithium.
7. Utilisation suivant l'une quelconque des revendications 1 à 6 d'un sel de lithium d'un acide gras essentiel.
8. Utilisation suivant l'une quelconque des revendications 4 à 7 pour la préparation de l'agent précité sous la forme d'une dose unitaire, chaque dose unitaire contenant de 100 à 1200 mg du composé de lithium précité.
9. Utilisation suivant l'une quelconque des revendications 1 à 8 pour la préparation de l'agent précité sous

la forme d'une dose unitaire, chaque dose unitaire contenant de 50 à 1200 mg de l'acide gras essentiel précité ou d'un sel de celui-ci.

Patentansprüche

- 5 1. Verwendung einer essentiellen Fettsäure oder physiologisch verträglicher Salze davon zur Herstellung eines therapeutischen Mittels zur Bekämpfung von Dementia praesentilis oder senilis.
- 10 2. Verwendung nach Anspruch 1 zur Herstellung eines therapeutischen Mittels zur Bekämpfung der Alzheimer Krankheit.
- 15 3. Verwendung nach einem der Ansprüche 1 oder 2, worin die essentielle Fettsäure oder das Salz davon ausgewählt ist unter Di-homo- γ -linolensäure, Arachidonsäure, Eikosapentaensäure, Docosahexaensäure, Linolsäure, γ -Linolensäure, α -Linolensäure, 18:4n-3 und der physiologisch verträglichen Salze davon.
- 20 4. Verwendung nach einem der Ansprüche 1 bis 3 einer physiologisch verträglichen Lithiumverbindung zusammen mit der essentiellen Fettsäure oder einem Salz davon.
- 25 5. Verwendung nach Anspruch 4, wobei die Lithiumverbindung ein Lithiumsalz ist.
6. Verwendung nach Anspruch 5, wobei das Lithiumsalz ausgewählt ist unter: Lithiumcarbonat, Lithiumcitrat, Lithiumsuccinat, Lithiumchlorid, Lithiumbromid, Lithiumacetat, Lithiumacetylsalicylat, Lithiumbenzoat, Lithiumbitartrat, Lithiumnitrat, Lithiumselenat, Lithiumselenit, Lithiumsulfat, Lithiumaspartat, Lithiumgluconat und Lithiumthenoat.
- 30 7. Verwendung nach einem der Ansprüche 1 bis 6 eines Lithiumsalzes einer essentiellen Fettsäure.
8. Verwendung nach einem der Ansprüche 4 bis 7, zur Herstellung des Mittels in Dosisform, wobei jede Dosisform 100 bis 1200 mg der Lithiumverbindung enthält.
- 35 9. Verwendung nach einem der Ansprüche 1 bis 8, zur Herstellung des Mittels in Dosisform, wobei jede Dosisform 50 bis 1200 mg der essentiellen Fettsäure oder des Salzes davon enthält.

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